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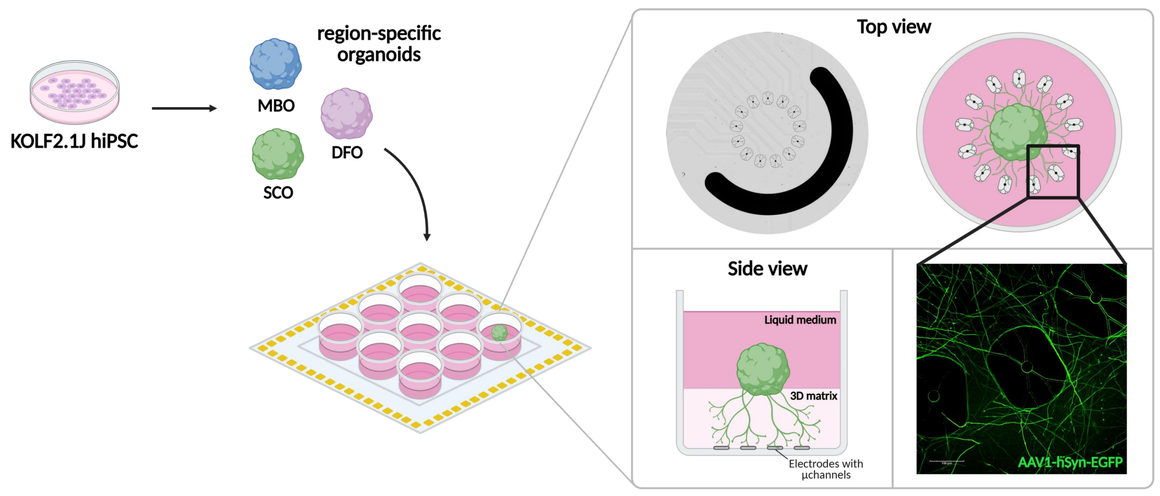
A glass-based microfluidic MEA platform for non-invasive, scalable electrophysiology of human neural organoids

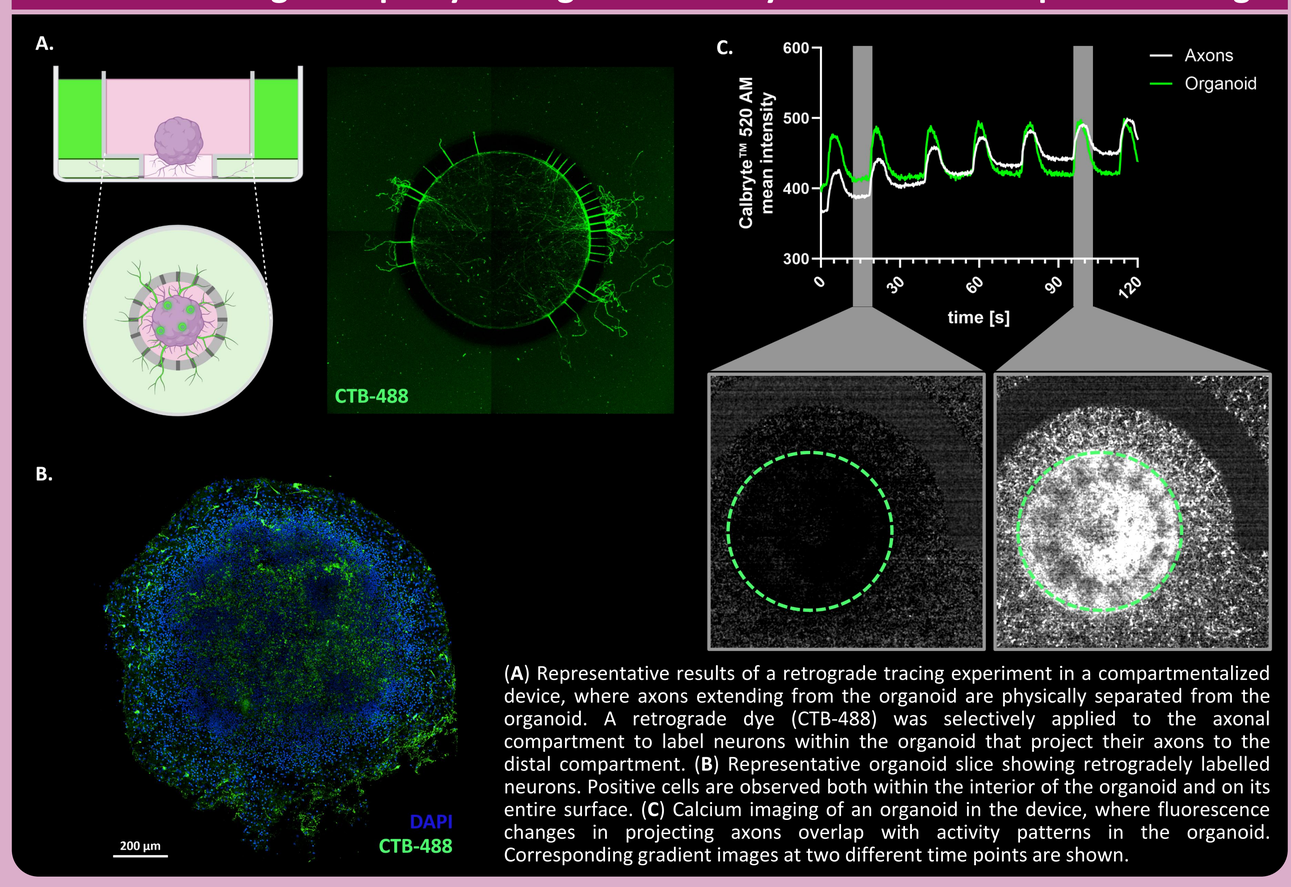
Background and aim

Human neural organoids in microfluidic systems are powerful 3D models of brain development, disease, and drug response. However, functional characterization remains challenging: conventional MEAs mainly capture surface activity, while 3D approaches often disrupt tissue integrity, limit growth, or lack scalability. Additionally, PDMS-based platforms are suboptimal for drug studies due to absorption of hydrophobic compounds[1].



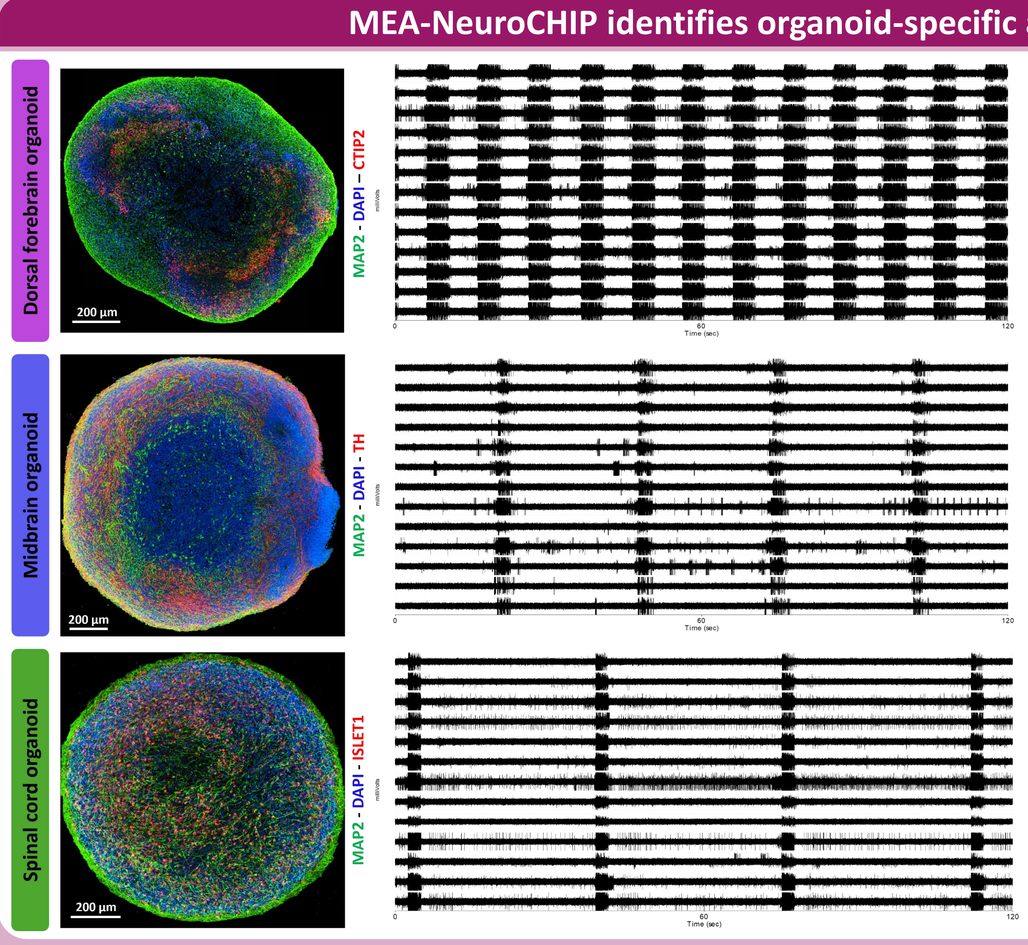
AIM: To develop and validate a scalable MEA-based organ-on-chip platform for electrophysiological recording and pharmacological testing of hiPSC-derived neural organoids, leveraging neurite-trapping electrode technology[2].

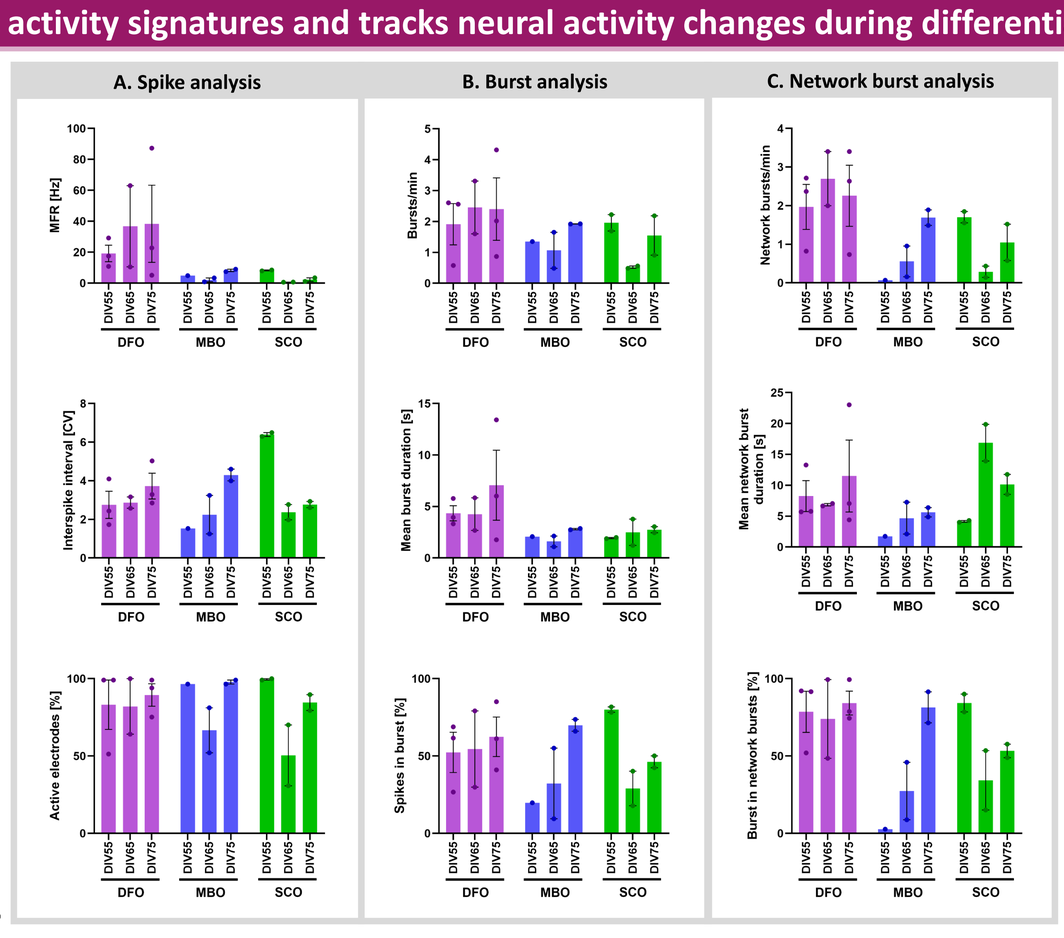
Axonal recordings as a proxy for organoid activity with enhanced spatial coverage



(**A**) Representative results of a retrograde tracing experiment in a compartmentalized device, where axons extending from the organoid are physically separated from the organoid. A retrograde dye (CTB-488) was selectively applied to the axonal compartment to label neurons within the organoid that project their axons to the distal compartment. (**B**) Representative organoid slice showing retrogradely labelled neurons. Positive cells are observed both within the interior of the organoid and on its entire surface. (**C**) Calcium imaging of an organoid in the device, where fluorescence changes in projecting axons overlap with activity patterns in the organoid. Corresponding gradient images at two different time points are shown.

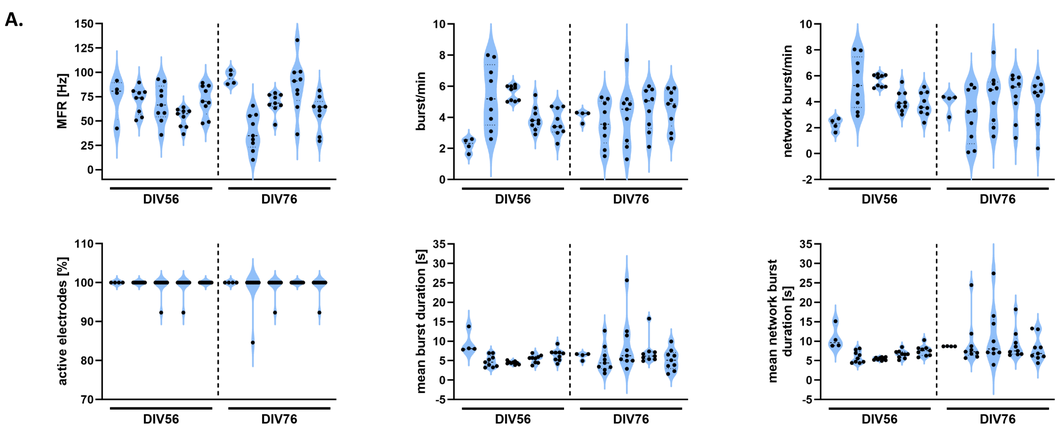
MEA-NeuroCHIP identifies organoid-specific activity signatures and tracks neural activity changes during differentiation

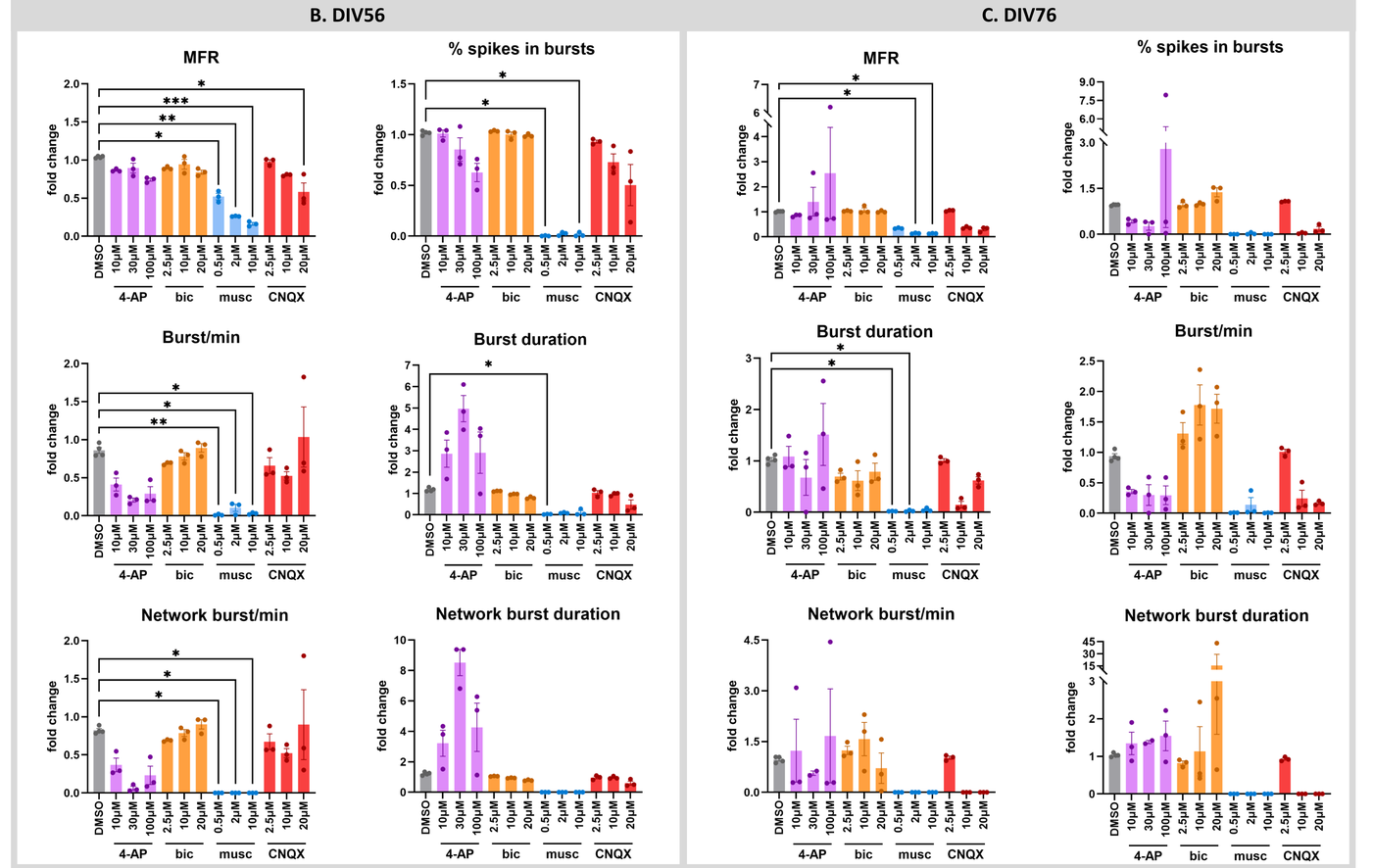




This figure shows representative immunostainings of dorsal forebrain (DFO), midbrain (MBO), and spinal cord organoids (SCO) confirming region-specific identity. Corresponding raw recordings from 13 electrodes per well (one organoid per well) show distinct activity patterns across organoid types. Electrophysiological activity was assessed at multiple differentiation stages (DIV55, DIV65, DIV75), with recordings performed 10 days after transfer to chips (n = 9 wells per chip). Each plotted data point represents the mean value across the 9 wells of each differentiation experiment. Data are shown as mean ± SEM. (**A**) Spikes were detected by template-based thresholding (4.75× median sigma) with ISI filtering (minimum 0.75 ms). (**B**) Bursts were identified using a Poisson Surprise method (≥10 spikes, ≥0.40 s, Surprise ≥4.5) with adaptive windowing and burst merging. (**C**) Network bursts were detected from burst median timestamps (≥3 events, Surprise ≥4.6, max window 1.5 s) and required ≥6 contributing electrodes (13 electrodes total); adjacent events were merged (≤0.8 s).

MEA recordings capture drug-induced neural activity changes across differentiation and show robust reproducibility across chips





(**A**) Comparison of electrophysiological parameters recorded from dorsal forebrain organoids cultured on 5 different chips at two differentiation time points (DIV56 and DIV76). Each chip contains organoids from the same differentiation batch, enabling assessment of reproducibility and consistency across devices. (**B**) Changes in electrophysiological parameters following application of selected pharmacological compounds that modulate neural activity, highlighting compound-specific effects on spiking, bursting, and network behaviour at DIV56. Parameters were detected in the same way as in the abovementioned figure description. (**C**) Drug-induced modulation of the same electrophysiological parameters at a later differentiation stage (DIV76), demonstrating maturation-dependent differences in pharmacological responses. Data are shown as mean ± SEM.

4-AP = 4-aminopyridine (K- channel blocker), **bic** = bicuculline ($GABA_A$ receptor antagonist), **musc** = muscimol ($GABA_A$ receptor agonist), **CNQX** (AMPA/kainate receptor antagonist)

Conclusion and outlook

The newly developed MEA-NeuroCHIP enables reproducible 3D recordings from hiPSC-derived brain organoids while preserving tissue integrity. It captures region-specific activity, neuronal network maturation, and supports sensitive pharmacological testing in a scalable, human-relevant 3D system, with strong potential for preclinical screening and personalized medicine.

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References:

[1] Toepke, Michael W, and David J Beebe. "PDMS absorption of small molecules and consequences in microfluidic applications." *Lab on a chip* vol. 6,12 (2006)

[2] Molina-Martínez, Beatriz et al. "A multimodal 3D neuro-microphysiological system with neurite-trapping microelectrodes." *Biofabrication* vol. 14,2 10.1088/1758-5090/ac463b (2022)